DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003N–0268]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Biological Products: Reporting of Biological Product Deviations in Manufacturing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: JonnaLynn P. Capezzuto, Office of Management Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Biological Products: Reporting of Biological Product Deviations in Manufacturing—(OMB Control Number 0910–0458)—Extension

Under section 351 of the Public Health Service Act (42 U.S.C. 262), all biological products, including human blood and blood components, offered for sale in interstate commerce must be licensed and meet standards designed to ensure the continued safety, purity, and potency of such products. In addition, section 501 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351) provides that drugs and devices (including human blood and blood components) are adulterated if they do not conform with current good manufacturing practice (CGMP) assuring that they meet the requirements of the act. All establishments manufacturing human blood and blood components are required to register with FDA, and comply with the CGMP regulations for human blood and blood components (parts 211 and 606 (21 CFR parts 211 and 606)). Transfusion services are required under 42 CFR 493.1273(a) to comply with part 606 and 21 CFR part 640 as they pertain to the performance of manufacturing activities. FDA regards biological product deviation reporting to be an essential tool in its directive to protect public health by establishing and maintaining surveillance programs that provide timely and useful information. Section 600.14 (21 CFR 600.14) requires the licensed manufacturer who holds the biological product license, for other than human blood and blood components, and who had control over the product when the deviation occurred, to report to the Center for Biologics Evaluation and Research (CBER) as soon as possible but not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has

occurred. Section 606.171 requires a licensed manufacturer of human blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the product when the deviation occurred, to report to CBER as soon as possible but not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has occurred. Respondents to this collection of information are the licensed manufacturers of biological products other than human blood and blood components, unlicensed registered blood establishments, and transfusion services. Based on information from CBER's databases for fiscal year (FY) 2002, there were 115 licensed manufacturers of biological products other than human blood and blood components, 207 licensed manufacturers of human blood and blood components, including Source Plasma, and 2,800 unlicensed registered blood establishments and 3,221 transfusion services. However, not all manufacturers or establishments may have any submissions in a given year and some may have multiple submissions. In the same FY, CBER's database also showed that the licensed manufacturers of biological products other than human blood and blood components submitted 476 biological product deviation reports (BPDRs) under § 600.14, the licensed manufacturers of human blood and blood components, including Source Plasma submitted 27,000 BPDRs under § 606.171, and the unlicensed registered blood establishments and transfusion services submitted a total of 6,446 BPDRs. The number of total annual responses is based on the number of BPDRs CBER received in FY 2002. The rate of submission is not expected to change significantly in the next few years. Based on information from industry, the estimated average time to complete a deviation report is 2 hours. The availability of the standardized report FDA Form 3486, and the

ability to submit this report electronically further streamlines the report submission process. Activities such as investigating, changing standard operating procedures (SOPs) or processes, and followup are currently required under parts 211 (approved under OMB control numbers 0910–0139 and 0910–0353), 606 (approved under OMB control number 0910–0116), and 820 (21 CFR part 820) (approved under OMB control number 0910–0073) and, therefore, are not included in the burden calculation for the separate requirement of submitting a deviation report to FDA.

In the **Federal Register** of June 30, 2003 (68 FR 38712), FDA published a 60-day notice requesting public comment on the information collection provisions. We received two comments.

In response to whether the proposed collection of information is necessary, comment one stated that we should harmonize the biological product deviation reporting requirements (§ 600.14) with the NDA field alert reports under 21 CFR 314.81(b)(1) and, therefore, revoke § 600.14. The comment stated the adoption of the new drug application (NDA) field alert regulations for all biologics would streamline compliance activities, and facilitate and align the recent transfer of biotechnology products from CBER to the Center for Drug Evaluation and Research (CDER). The comment also stated that revocation of § 600.14 would reduce the reporting burden while continuing to support the industry in making good, risk based quality decisions.

The NDA field alert regulations (approved under OMB control number 0910–0001) are applicable only to those products that are approved for marketing under the provisions of part 314 (21 CFR part 314) (including those few products that CBER regulates even though they were approved under the NDA provisions of part 314). The NDA field alert regulations do not apply

to biological drug products subject to licensing under the Public Health Service (PHS) Act, including licensed products that CDER now regulates. FDA has harmonized a number of regulations for certain biotechnology products where products regulated as biological products subject to licensure are similar to products subject to regulation as new drugs (see 65 FR 66621 at 66625, November 7, 2000). The products recently transferred from CBER to CDER are still regulated as biological products under the PHS Act. However, we recently stated in our CBER Web site that the biological product deviation reports for those transferred products are now to be sent to CDER. CBER will continue to monitor and assess its biological product deviation reporting program. If the level of reporting or the needs of the agency change, FDA will consider whether to harmonize its reporting requirements. The comment's suggestion that FDA adopt the NDA field alert regulations in § 314.81(b)(1) and revoke § 600.14 seeks a regulatory change that is outside the scope of FDA's current request for OMB renewal of the information collection in the existing regulations. Consequently, we decline to adopt the comment's recommendations.

Comment two, in response to the necessity of the proposed regulation, recommended revisions to the regulation regarding the submission of reports regarding post-donation information, and argued that only a small percentage of those reports were forwarded to District Offices for further investigation and that the reporting burden has resulted in little tangible outcome. FDA uses those reports for reasons other than initiating further investigation or product recalls. For example, some reports of post-donation information revealed to FDA that the manufacturers had flaws in their donor screening procedures, which FDA communicated to the companies. In addition, information from

biological product deviation reports has been valuable to FDA in crafting guidances for industry that improve product quality and reduce manufacturing problems generally. However, we will continue to monitor and assess our biological product deviation reporting program, including the review of these type of reports. Consequently, we decline to adopt the comment's recommendations at this time.

In response to FDA's burden estimate, comment one questioned the estimated hours per response to submit a report to FDA and stated that FDA's estimate did not factor in the time to completely process the report. The comment provided an estimation of burden hours to submit a report 10 times FDA's estimate. In addition, the comment stated that additional time is required to update SOPs associated with the regulation and to perform ongoing training.

Based on comments received in response to the burden hours published in the proposed rule of September 23, 1997 (62 FR 49642), FDA revised the burden hours (hours per response) in the final rule (65 FR 66621 at 66632, November 7, 2000) to the current estimate. In response to the comments on the proposed rule, we stated the revised estimate was based in part on information from industry representatives about typical procedures, and the availability of a standardized report form. Activities such as investigating, changing SOPs or processes, and followup are required under parts 211, 606, and 820, and therefore, are not included in the burden estimate for the separate requirement of submitting to FDA a biological product deviation report. In the final rule, we estimated the hours as a one-time burden, in part, for establishing and making adjustments to SOPs and staff training. Continuance of these

activities would be considered as part of normal business practice or covered by other regulations. We, therefore, decline to revise the burden hours.

Comment two questioned FDA's estimate that the rate of submissions was not expected to change significantly in the next few years. The comment stated that there was a large increase in the number of reports from the previous year.

We realize that the number of reports increased in the first couple of years after issuance of the final rule as industry adjusted to the new reporting requirements. However, we expect the numbers of reports to level off after this adjustment period, and therefore, we estimate that the rate of submission will not significantly increase in the next few years. If the number of reports significantly increases unexpectedly in the next few years, we will adjust the estimates at the next interval for approval of the information collection. Consequently, we decline to revise the estimates at this time.

In response to ways of minimizing the collection burden, comment one stated that we should notify manufacturers when a report is submitted that is not deemed to meet the threshold for reporting. The comment also stated that firms are not comfortable with filing submissions electronically because there are inadequate safeguards to ensure against false reports.

For reports submitted electronically, we notify the manufacturer of those reports that do not meet the threshold for reporting. For those submitted in hard copy, we notify the manufacturer if a trend of a particular type of unnecessary report is detected. We currently have an approximate rate of 45 percent of reports submitted electronically with the majority being submitted by the blood industry. Because the system is designed with a user name and password that is associated with the establishment, we believe there are adequate safeguards for submitting the information electronically.

Comment two responded to ways of minimizing the collection burden by recommending that post-donation information be reported in summary format not to exceed annually. Although, as mentioned previously, FDA has made valuable use of promptly-reported post-donation information, we will continue to monitor and assess our biological product deviation reporting program and make adjustments accordingly.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	Form No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
600.14	3,486	115	4.1	476	2	952
606.171[2]	3,486	207	130.4	27,000	2	54,000
606.171[3]	3,486	6,021	1.1	6,446	2	12,892
Total						67,844

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Licensed manufacturers of human blood and blood components, including Source Plasma.
[3] Unlicensed registered blood establishments and transfusion services (2,800 + 3,221 = 6,021).

Dated: December 16, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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